



Neuropathic Pain

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Post-herpetic Neuralgia (PHN)	Diabetic Peripheral Neuropathy (DPN)	Neuropathic Pain	Fibromyalgia	Other indications
capsaicin OTC ¹	generic			X		Treatment of mild to moderate pain
duloxetine (Cymbalta®) ²	generic		X	X	X	Major depressive disorder, generalized anxiety disorder, chronic musculoskeletal pain
gabapentin (Neurontin®) ³	generic	X (in adults)				Adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy, adjunctive therapy in the treatment of partial seizures in pediatric patients age 3–12 years
gabapentin (Gralise™) ⁴	Depomed	X (in adults)				
gabapentin enacarbil (Horizant™) ⁵	Xenoport	X (in adults)				Treatment of moderate-to-severe primary Restless Legs Syndrome in adults.
lidocaine (Lidoderm®) ⁶	generic	X				
lidocaine/ allantoin/ petrolatum (Vexa) ⁷	Pharmaceutical North America					<ul style="list-style-type: none"> Scar management Temporarily protects minor cuts, scrapes and burns Temporarily relief of pain associated with minor cuts, scrapes and minor skin irritations

FDA-Approved Indications (cont.)

Drug	Manufacturer	Post-herpetic Neuralgia (PHN)	Diabetic Peripheral Neuropathy (DPN)	Neuropathic Pain	Fibromyalgia	Other indications
milnacipran (Savella™) ⁸	Forest				X (in adults)	
pregabalin (Lyrica®) ⁹	Pfizer	X	X	X (associated with spinal cord injury)	X	Partial onset seizures as adjunctive therapy
tapentadol ER (Nucynta ER®) ¹⁰			X (in adults)			

OTC = over-the counter

Capsaicin (Qutenza®) 8% patch, manufactured by NeurogesX, is indicated for the management of neuropathic pain associated with post-herpetic neuralgia.¹¹ Administration by a health care professional in an office/clinic setting is required.

OVERVIEW^{12,13,14,15,16,17}

Neuropathic pain can be caused by a number of different diseases (e.g., diabetes mellitus, herpes zoster, human immunodeficiency virus [HIV] infection), medical interventions (e.g., chemotherapy, surgery), and injuries. It has recently been defined as the pain that evolves as a result of direct injury or disease to the nervous system, specifically the somatosensory system.

Neuropathic pain is commonly associated with diabetic peripheral neuropathy (DPN) and post-herpetic neuralgia (PHN). This review will have a concentration on post herpetic neuralgia, diabetic peripheral neuropathy, neuropathic pain in general, and fibromyalgia.

Post-Herpetic Neuralgia

Post-Herpetic Neuralgia (PHN) is a long-lasting pain disorder that causes pain from stimuli that are not normally painful. There are a number of oral medications available to treat neuropathic pain. The current 2004 American Academy of Neurology treatment guidelines advise that tricyclic antidepressants, gabapentin, pregabalin (Lyrica), opioids, and lidocaine transdermal patches (Lidoderm) can be used as the first option in treating PHN.¹⁸

Diabetic Peripheral Neuropathic Pain and Neuropathic Pain^{19,20,21,22,23,24}

Diabetic peripheral neuropathic pain (DPNP) is a common complication of diabetes mellitus. The etiology, though not completely understood, is thought to be multifactorial. The most common symptoms associated with DPNP are pain or loss of feeling in the toes, feet, legs, and arms. DPNP can affect many aspects of life and severely limit the patient's daily functions. Loss of sensation in the periphery may lead to muscle weakness and loss of reflexes, especially in the ankles, which can lead to gait disturbances. Patients with DPNP may be unaware of pressure or injury, leading to blisters or sores appearing on numb areas of the foot or leg. These areas may go unnoticed for extended periods of time, increasing the risk for infection and possibly amputation.

Diagnosis of DPNP is based on the presence of symptoms and a physical exam. A comprehensive foot exam is performed to assess skin appearance and integrity, muscles, bones, circulation, and sensation of the feet. Pin prick sensation, vibration perception, 10-g monofilament pressure sensation, and assessment of ankle reflexes are commonly performed tests used to screen, diagnose, and assess DPNP. General treatment measures include glycemic control, foot care, and the treatment of pain.

Current consensus guidelines (2006) from the Mayo Clinic recommend duloxetine (Cymbalta), as well as oxycodone CR (Oxycontin®), pregabalin (Lyrica), and tricyclic antidepressants as first-tier agents for the treatment of DPNP.²⁵ Duloxetine is not recommended for patients with hepatic insufficiency or where drug interactions are a factor. Duloxetine is a naphthalene derivative that is converted to naphthol in acidic environments. Even though duloxetine is enteric coated, conversion may occur with delayed gastric emptying, such as with diabetic gastroparesis which is due to autonomic nerve toxicity.²⁶ Naphthol is also known to cause ocular toxicity which may be of concern in diabetics.²⁷ Venlafaxine ER (Effexor® XR, venlafaxine extended-release tablets), along with tramadol (Ultram®) and antiepileptics, such as carbamazepine, gabapentin, and lamotrigine, are identified as second-tier agents. These guidelines were supported by a grant from the manufacturer of duloxetine.

According to the 2011 American Academy of Neurology Guidelines for the management of diabetic neuropathic pain, treatments include pregabalin (Level A recommendation) which is established as effective and amitriptyline, duloxetine, venlafaxine, gabapentin, valproate, opioids (morphine sulfate, oxycodone controlled-release, or tramadol), or topical capsaicin (all Level B recommendations) which are probably effective.²⁸ Effective treatments for painful diabetic neuropathy are available, but many have adverse effects that limit their usefulness, and few studies have adequate information on treatment effects on function and quality of life.

Recently, tapentadol ER (Nucynta ER) gained the indication for the management of neuropathic pain associated with diabetic peripheral neuropathy in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

Medication selection should be individualized, considering adverse effects, potential beneficial or deleterious effects on comorbidities, and whether prompt onset of pain relief is necessary.

Fibromyalgia

Fibromyalgia is a chronic disorder characterized by pain, fatigue, and sleep disturbances. It predominantly affects women and is difficult to treat. A multidisciplinary approach should be utilized. In 2010, the American College of Rheumatology (ACR) updated the diagnostic criteria for fibromyalgia. Although the presence of widespread pain is still needed for diagnosis, a specific number of tender points is no longer required. Rather, a widespread pain index (WPI) and symptom severity scale (SS), which includes somatic symptoms, waking unrefreshed, cognition, and fatigue, is employed.²⁹ Symptoms must have been present for at least three months and cannot be explained by another medical condition. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia. Laboratory tests for thyroid stimulating hormone (TSH) and erythrocyte sedimentation rate (ESR) are recommended to rule out hypothyroidism and polymyalgia rheumatica, respectively, as they have similar symptomatology.

Tricyclic antidepressants (TCAs), a class of drugs not approved for the treatment of fibromyalgia, have been found to be effective in a couple of trials of short duration.^{30,31} These drugs are associated with a number of adverse effects including anticholinergic effects (e.g., dry mouth and urinary retention),

orthostatic hypotension, and cardiac dysfunction. Gabapentin is not approved for the treatment of fibromyalgia, though its effectiveness in the treatment of fibromyalgia is supported by data.³² Gabapentin has low bioavailability and is not rapidly absorbed; therefore, it requires a dosage regimen of three to four times daily. The American Pain Society (APS) last produced guidelines for fibromyalgia pain treatment in 2005, prior to any product receiving FDA approval for treatment of this condition.³³ FDA-approved drugs for the treatment of fibromyalgia now include duloxetine (Cymbalta), milnacipran (Savella), and pregabalin (Lyrica). The APS guidelines recommend amitriptyline (and other TCAs) or cyclobenzaprine as the initial pharmacologic option, with selective serotonin reuptake inhibitors (SSRIs), tramadol, and opioids also listed as subsequent options. Amitriptyline and cyclobenzaprine received the highest ranking regarding strength and consistency of evidence at the time. There is no comparative evidence to support the superiority of any of these products in fibromyalgia.

PHARMACOLOGY^{34,35,36,37,38,39,40}

Drug Mechanism of Action	Mechanism of Action
capsaicin (OTC)	Capsaicin causes an initial enhanced stimulation of transient receptor potential vanilloid 1 (TRPV1), expressed on nociceptive nerve fibers in the skin. This stimulation may result in painful sensations, which are followed by pain relief thought to be mediated by a reduction in TRPV1-expressing nociceptive nerve endings.
duloxetine (Cymbalta)	Potential of serotonergic and noradrenergic activity in the central nervous system (CNS).
gabapentin (Gralise, Neurontin)	Gabapentin binds to the presynaptic $\alpha 2$ -delta subunit of voltage sensitive calcium channels.
gabapentin enacarbil (Horizant)	Gabapentin enacarbil is a prodrug of gabapentin; gabapentin binds to the presynaptic $\alpha 2$ -delta subunit of voltage sensitive calcium channels.
lidocaine (Lidoderm)	Stabilizes neuronal membranes by inhibiting the ionic fluxes required for initiation and conduction of impulses.
lidocaine/ allantoin/ petrolatum (Vexa) ⁴¹	Lidocaine: Stabilizes neuronal membranes by inhibiting the ionic fluxes required for initiation and conduction of impulses. Allantoin: antibacterial, keratolytic, astringent, and moisturizing properties which lead to cell-proliferation and removal of necrotic tissue.
milnacipran (Savella)	Potential of serotonergic and noradrenergic activity in the CNS. The exact mechanism of the central pain inhibitory action of milnacipran and its ability to improve the symptoms of fibromyalgia is unknown.
pregabalin (Lyrica)	Pregabalin binds to presynaptic $\alpha 2$ -delta subunit of voltage sensitive calcium channels, inhibiting release of pro-nociceptive neurotransmitters in the spinal cord.
tapentadol ER (Nucynta ER)	Tapentadol is a centrally-acting synthetic analgesic. The exact mechanism of action is unknown. Although the clinical relevance is unclear, preclinical studies have shown that tapentadol is a mu-opioid receptor (MOR) agonist and a norepinephrine reuptake inhibitor (NRI).

PHARMACOKINETICS^{42,43,44}

Systemic absorption of the topical agents is low. No detectable levels of capsaicin metabolites were observed in treated patients. The duration of action of capsaicin cream is about four to six hours, with maximal pain relief occurring with two weeks of continuous therapy.

Lidocaine (Lidoderm) has varied absorption depending on the duration of application and the surface area over which it is applied. Only three percent (\pm two percent) of the applied dose is expected to be systemically absorbed. At least 95 percent of lidocaine within the patch system will remain in a used patch. Lidocaine is approximately 70 percent protein bound. However, at higher concentrations, the binding becomes concentration-dependent. Metabolism in the skin is unknown; however, lidocaine is metabolized rapidly by the liver to a number of metabolites which are then renally excreted.

In a small study (n=6) to test skin penetration, two applications of allantoin 1% solution absorption in oil/water cream was made to the inner forearm of subjects. One application was left in place for three hours the other for six hours. Allantoin penetration was 13 and 15.4 percent respectively. Allantoin is excreted in urine unchanged.

Drug	Bioavailability (%)	Tmax (hrs)	Half-life (hrs)	Active metabolites	Excretion (%)
duloxetine (Cymbalta) ⁴⁵	N/A	6	12	None	Urine: 70 Feces: 20
gabapentin (Neurontin) ⁴⁶	27-60 (not dose proportional)	2-4	5-7	None	Renal
gabapentin (Gralise) ⁴⁷	N/A	8	5-7	None	Renal
gabapentin enacarbil (Horizant) ⁴⁸	42-65 (fasting state) 75 (fed state)	5 (fasting state) 7.3 (fed state)	5.1-6	Yes	Renal
milnacipran (Savella) ⁴⁹	85-90	2-4	6-8	None	Urine: 55
pregabalin (Lyrica) ⁵⁰	>90	1.5	6	None	Urine: 90-98
tapentadol ER (Nucynta ER) ⁵¹	– 32	– 3-6	5	– None	– Renal

N/A = not available

*Both Gralise and Horizant are not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration.

CONTRAINDICATIONS/WARNINGS^{52,53,54,55,56,57,58}

Capsaicin (OTC) has no contraindications. Capsaicin should not be used near eyes, mucus membranes, or near skin with abrasions, irritation, infection, or inflammation. If irritation does occur, flush the affected area with water. Inhalation of airborne capsaicin following patch removal or removal of clothing covering capsaicin cream can cause coughing or sneezing. Blood pressure may increase transiently during and after capsaicin administration and should be monitored. Patients should be prepared to treat acute pain during and following capsaicin application with local cooling or appropriate analgesics. Treated areas may become heat-sensitive following application.

Used lidocaine patches (Lidoderm) will still contain a large amount of lidocaine (at least 665 mg). To avoid accidental exposure of children, pets, and others, proper storage and disposal of lidocaine patches is highly recommended. Use of lidocaine with external heating sources, such as heating pads or electric blankets, should be avoided. Extended duration of application of lidocaine-containing patches (Lidoderm, **Vexa**), application of more than the recommended number of patches, use in smaller patients, or use in patients with impaired elimination may lead to increased blood concentrations of lidocaine and serious adverse effects.

Lidocaine/allantoin/petrolatum patch (Vexa) should not be used on deep puncture wounds, animal bites, or serious burns, and should not be used in large quantities, particularly over raw surfaces or blistered areas. Lidocaine/allantoin/petrolatum patches are contraindicated in patients with a hypersensitivity to local amide anesthetics, as well as any other component of the product.⁵⁹

In 2008, the Food and Drug Administration (FDA) informed healthcare professionals that the Agency had analyzed reports of suicidality (suicidal behavior or ideation) from placebo-controlled clinical studies of 11 drugs used to treat epilepsy, as well as psychiatric disorders and other conditions.⁶⁰ The FDA's analysis stated that patients receiving antiepileptic drugs had approximately twice the risk of suicidal behavior or ideation (0.43 percent) compared to patients receiving placebo (0.22 percent). The increased risk of suicidal behavior and suicidal ideation was observed as early as one week after starting the antiepileptic drug and continued through 24 weeks. The results were generally consistent among the 11 drugs. Gabapentin (Neurontin) and pregabalin (Lyrica) were among those that were included in the analysis. The relative risk for suicidality was higher in patients with epilepsy compared to patients who were given one of the drugs in the class for psychiatric or other conditions.

Health care professionals should closely monitor all patients currently taking or starting any antiepileptic drug, including gabapentin (Neurontin, Gralise), gabapentin enacarbil (Horizant), and pregabalin (Lyrica) for notable changes in behavior that could indicate the emergence or worsening of suicidal thoughts, behavior, or depression.

Duloxetine (Cymbalta) and milnacipran (Savella) also have black box warnings regarding the risk of suicide. Like other antidepressants, including serotonin-norepinephrine reuptake inhibitors (SNRIs), these agents increase the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder and other psychiatric disorders. Healthcare professionals considering the use of any antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need.

Duloxetine and milnacipran are contraindicated in patients with uncontrolled narrow-angle glaucoma. Concomitant use of duloxetine with monoamine oxidase inhibitors (MAOIs) is also contraindicated.

Treatment with SNRIs, including duloxetine and milnacipran, relative to placebo has been associated with increases in blood pressure. Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment. However, orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine, especially during the first week of therapy or after dose increases. The risk of decreased blood pressure may be greater in patients taking concomitant medications that induce orthostatic hypotension or are potent CYP1A2 inhibitors and in patients taking duloxetine at doses above 60 mg daily. Consider discontinuation of duloxetine in patients with symptomatic orthostatic hypotension and/or syncope during duloxetine therapy.

The development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome-like reaction may occur with SNRI treatment, particularly with concomitant use of serotonergic drugs, including triptans, and drugs that impair metabolism of serotonin, including MAOIs. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

SNRIs, including duloxetine and milnacipran, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may increase this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding.

Duloxetine and milnacipran have been known to affect urethral resistance. If symptoms of urinary hesitation develop, consideration should be given to the possibility that it might be drug-related.

Duloxetine and milnacipran should not be prescribed for patients with substantial alcohol use or evidence of chronic liver disease. Elevated transaminases, bilirubin, and other liver function markers have occurred when SNRIs have been given to such patients. There have been reports of hepatic failure in patients treated with either duloxetine or milnacipran.

Duloxetine (Cymbalta) should not be used concomitantly within two weeks of stopping an MAOI. Additionally, when converting from an MAOI to duloxetine, there must be a washout period of seven to 14 days.

Due to the risk of serotonin syndrome, milnacipran is also contraindicated with concomitant use with MAOIs used for the treatment of psychiatric disorders. If treatment with an MAOI is absolutely necessary, milnacipran should be discontinued five days prior to initiating a MAOI or 14 days should elapse before discontinuation of an MAOI and initiation of milnacipran.

Heart rate should be measured at baseline prior to the initiation of milnacipran treatment and periodically thereafter. For patients who experience a sustained increase in heart rate while receiving milnacipran, dose reduction or discontinuation of milnacipran may be clinically warranted.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), a multi-organ hypersensitivity reaction, has occurred with gabapentin (Gralise, Horizant, Neurontin). Some cases have been fatal or life threatening. Manifestations of DRESS typically include fever, rash, and/or lymphadenopathy in conjunction with other organ system abnormalities including hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis.

Gabapentin may cause somnolence/sedation and dizziness. Patients should be cautioned when driving or operating a car or other complex machinery until sufficient experience is gained to assess the ability to perform these tasks.

Gabapentin and pregabalin (Lyrica) should be gradually withdrawn over at least a one-week period to minimize the potential of increased seizure frequency. A gradual reduction in the dose of SNRIs, including duloxetine and milnacipran, rather than abrupt cessation is also recommended whenever possible.

Peripheral edema is a concern with pregabalin. There have been post-marketing reports of angioedema in patients during initial and chronic treatment with pregabalin. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). There were reports of life-threatening angioedema with respiratory compromise requiring emergency treatment.

Tapentadol ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma, paralytic ileus, and in patients concurrently using MAOIs or patients who have used MAOIs in the past 14 days.

Tapentadol ER is a Schedule II controlled substance. It has a boxed warning regarding abuse potential, life-threatening respiratory depression, accidental exposure, and interaction with alcohol. There is also a warning regarding the interaction of tapentadol with CNS depressants. A dose reduction of tapentadol ER or the inferior drug should be considered. Tapentadol ER is cautioned in patients with a history of seizures. Serotonin syndrome could result from other medications that exhibit serotonergic activity.

Gabapentin is not a scheduled drug but recent post-marketing reports point to misuse and abuse.⁶¹ The patient's drug abuse history must be evaluated prior to prescribing gabapentin, and the patient must be observed for signs and symptoms.

Medication Guide/Risk Evaluation and Mitigation Strategies (REMS)

Duloxetine, gabapentin, milnacipran, and pregabalin prescriptions are dispensed with a medication guide. Tapentadol ER has been placed into the "ER/LA Opioid Analgesic REMS Program." This REMS uses a single, shared system for the elements to assure safe use and the REMS assessments.⁶²

DRUG INTERACTIONS^{63,64,65,66,67,68,69,70}

No drug interactions have been reported with capsaicin.

Lidocaine-containing patches (Lidoderm, Vexa) should be used with caution in patients receiving Class I antiarrhythmics (e.g., tocainide and mexiletine) since the toxic effects are additive and potentially synergistic. In addition, caution should also be exercised when using lidocaine-containing patches with other products containing local anesthetics.

Duloxetine (Cymbalta) should not be used concomitantly within two weeks of stopping an MAOI. Additionally, when converting from an MAOI to duloxetine, there must be a washout period of seven to 14 days.

Milnacipran should not be started in a patient being treated with linezolid or intravenous methylene blue because there is increased risk of serotonin syndrome.

Duloxetine is a moderate inhibitor of CYP2D6 and is also affected by inhibitors of CYP2D6 and CYP1A2 (increased duloxetine levels), and may impact the metabolism of other drugs metabolized by CYP2D6. Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, duloxetine and thioridazine should not be co-administered. Drugs that raise the gastric pH may lead to early release of duloxetine when given concomitantly. Duloxetine is highly protein bound and administration with another highly protein bound drug may increase free concentrations of the other drug.

Antacids may reduce the bioavailability of gabapentin (n=16) by approximately 20 percent. It is recommended that gabapentin be taken at least two hours following antacids containing aluminum and magnesium administration.

The development of a potentially life-threatening serotonin syndrome may occur with duloxetine and milnacipran (Savella) treatment, particularly with concomitant use of serotonergic drugs, including triptans, and with drugs which impair metabolism of serotonin, including MAOIs. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Concomitant use of these agents with a triptan requires careful observation of the patient, particularly during treatment initiation and dosage increases. Concomitant treatment with duloxetine and milnacipran with serotonergic or anti-dopaminergic agents, including antipsychotics, should be discontinued immediately if signs of serotonin syndrome and/or neuroleptic malignant syndrome emerge. These symptoms may include mental status changes, autonomic instability, neuromuscular aberrations, and/or gastrointestinal symptoms. Supportive symptomatic treatment should be initiated immediately. In addition, there is an increased risk of serotonin syndrome in patients treated with linezolid or intravenous methylene blue while on duloxetine therapy. Duloxetine should not be taken concomitantly unless acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits are judged to outweigh the risks. The patient should be monitored for symptoms of serotonin syndrome for five days or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first.

Milnacipran inhibits the reuptake of norepinephrine; therefore, concomitant use of milnacipran with epinephrine and norepinephrine may be associated with paroxysmal hypertension and possible arrhythmia.

Given the primary CNS effects of duloxetine and milnacipran, caution should be used when either is taken in combination with other centrally acting drugs, including those with a similar mechanism of action.

In a drug-drug interaction study, an increase in euphoria and postural hypotension was observed in patients who switched from clomipramine to milnacipran.

Use of milnacipran concomitantly with digoxin may be associated with potentiation of adverse hemodynamic effects. Postural hypotension and tachycardia have been reported in combination therapy with intravenously administered digoxin. Co-administration of milnacipran and intravenous digoxin should be avoided.

Because milnacipran inhibits norepinephrine reuptake, co-administration with clonidine may inhibit clonidine's anti-hypertensive effect.

Since pregabalin (Lyrica) is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2 percent of a dose recovered in urine as metabolites), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. In vitro and in vivo studies showed that pregabalin is unlikely to be involved in significant pharmacokinetic drug interactions.

Concomitant use of alcohol can increase plasma levels of tapentadol ER. Alcohol should be avoided while on tapentadol ER. MAOIs should not be taken within 14 days of using tapentadol ER. Concurrent use of tapentadol ER and other CNS depressants, including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, and alcohol, can increase the risk of respiratory depression, hypotension, profound sedation, or coma. The concomitant use of tapentadol ER with mixed agonist/antagonists (e.g., butorphanol, nalbuphine, and pentazocine) and partial agonists (e.g., buprenorphine) may precipitate withdrawal symptoms, and anticholinergic products may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

ADVERSE EFFECTS

Drug	Pruritis	Dermatitis	Burning	Nausea	Dysgeusia	Headache
capsaicin OTC ⁷¹	nr	nr	reported	nr	nr	nr
lidocaine (Lidoderm, Vexa) ^{72,73}	reported	reported	reported	reported	reported	Reported

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

Drug	Weight change	Nausea	Diarrhea	Somnolence	Dizziness	Dry mouth	Constipation	Edema	Tremor
duloxetine (Cymbalta) ⁷⁴	-0.6 kg	24	9	12	10	11	11	nr	2
gabapentin (Neurontin) ⁷⁵	reported	3.9	5.7	21.4	28	4.8	3.9	8.3	Reported
gabapentin (Gralise) ⁷⁶	reported	nr	3.3	4.5	10.9	2.8	1.4	3.9	Reported
gabapentin enacarbil (Horizant) ⁷⁷	reported	4-9	nr	10-14	17-30	reported	nr	6-7	Nr
milnacipran (Savella) ⁷⁸	-0.8 kg	35-39	reported	reported	10-11	5	15-16	reported	2
pregabalin (Lyrica) ⁷⁹	reported	reported	nr	4-16	8-29	2-7	2-6	4-12	1-2

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive.
nr = not reported.

Gabapentin (Neurontin) has an 8.3 percent incidence of nystagmus compared to four percent for placebo.⁸⁰

There have been post-marketing reports of angioedema in patients during initial and chronic treatment with pregabalin (Lyrica). Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). Additionally, there have been reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. Pregabalin should be discontinued immediately in patients with these symptoms. Exercise caution when prescribing pregabalin to patients with a history of angioedema or who are already taking medications associated with angioedema, such as angiotensin-converting enzyme (ACE) inhibitors.

The most common (≥ 10 percent) adverse reactions reported with tapentadol ER were nausea, constipation, dizziness, headache, and somnolence.⁸¹

SPECIAL POPULATIONS^{82,83,84,85,86,87,88}

Pediatrics

Safety and effectiveness in pediatric patients for the topical products in this review have not been established.

The use of pregabalin (Lyrica), milnacipran (Savella), duloxetine (Cymbalta), and tapentadol ER (Nucynta ER) have not been adequately studied in children.

Gabapentin (Neurontin) is indicated for treatment of partial seizures in children 12 years of age and older with epilepsy and as adjunctive therapy for treatment of partial seizures in children three to 12 years of age with epilepsy. The safety and effectiveness of gabapentin (Gralise, Horizant, Neurontin) in the management of postherpetic neuralgia in patients less than 18 years of age has not been studied.

Pregnancy

Capsaicin (OTC), lidocaine patch (Lidoderm), and lidocaine/allantoin/petrolatum (Vexa) patch are Pregnancy Category B.

Pregabalin (Lyrica), milnacipran (Savella), and duloxetine (Cymbalta) are Pregnancy Category C. Neonates exposed to SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding.

Although classified as Pregnancy Category C, gabapentin (Gralise, Horizant, Neurontin) has not been evaluated for use during pregnancy.

Tapentadol ER (Nucynta ER) is Pregnancy Category C. It should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Renal impairment

Duloxetine (Cymbalta) is not recommended for patients with end stage renal disease (ESRD) or severe renal impairment (estimated creatinine clearance < 30 mL/min).

Dosage adjustments are recommended for gabapentin (Gralise, Horizant, Neurontin) in patients with compromised renal function. Gabapentin has not been studied in pediatric patients with renal insufficiency.

Milnacipran (Savella) dose adjustment is necessary in patients with severe renal impairment.

Pregabalin (Lyrica) is excreted primarily by the renal route; therefore, dosage should be adjusted based on renal function as determined by creatinine clearance.

Tapentadol ER (Nucynta ER) is not recommended in patients with severe renal impairment due to accumulation of a metabolite formed by tapentadol.

Hepatic impairment

Patients with severe hepatic disease are at greater risk of developing toxic blood concentrations of lidocaine (Lidoderm, **Vexa**) because of their inability to metabolize lidocaine normally.

Duloxetine (Cymbalta) and milnacipran (Savella) should not be administered to patients with severe hepatic insufficiency as these products increase the risk of elevation of serum transaminase levels.

Use of tapentadol ER (Nucynta ER) is not recommended in severe hepatic impairment. The dose of tapentadol ER should be reduced in patients with moderate hepatic impairment.

DOSAGES

Drug	Initial dose	Maximum dose	Availability
capsaicin ⁸⁹	Apply topically up to five applications daily to affected areas	Wash hands with soap and water after applying	0.025, 0.035 0.075, 0.1, 0.25% cream 0.025% patch 0.035% lotion 0.15% liquid
duloxetine (Cymbalta) ⁹⁰	DPN: 60 mg once daily Fibromyalgia: 30 mg once daily Chronic musculoskeletal pain: 30 mg once daily	60 mg once daily	20, 30, 60 mg capsules
gabapentin (Neurontin) ⁹¹	300 mg three times a day	3,600 mg/day (three times a day); up to 50 mg/kg/day (pediatric dose)	100, 300, 400 mg capsules 600, 800 mg tablets 250 mg/5 mL solution
gabapentin (Gralise) ⁹²	300 mg/day	1,800 mg/day (once daily)	300, 600 mg tablets
gabapentin enacarbil (Horizant) ⁹³	600 mg/day for 3 days	600 mg twice daily	600 mg tablets

Dosages (continued)

Drug	Initial dose	Maximum dose	Availability
lidocaine (Lidoderm) ⁹⁴	Apply up to 3 patches to affected area once daily for up to 12 hours within a 24-hour period	Hand washing required after handling, and eye contact should be avoided Used patches should be folded on the adhesive side and discarded out of the reach of children and pets	5% patch
lidocaine/ allantoin/ petrolatum (Vexa) ⁹⁵	Apply one patch to affected area for up to eight hours in a 24 hour period. Use one patch at a time, up to four patches per day. Do not use patches for longer than five consecutive days. Patch should be applied to intact skin to cover the most painful area. Patches may be cut into smaller sizes prior to removal from release liner.	Apply immediately after removal from the protective envelope. Used patches should be folded on the adhesive side and discarded out of the reach of children and pets. Wash hands after handling, and eye contact should be avoided.	lidocaine 4% /allantoin 2% / petrolatum 30% patch
milnacipran (Savella) ⁹⁶	12.5 mg daily, titrated up to 50 mg twice daily over the course of one week	100 mg twice daily	12.5, 25, 50, 100 mg tablets 4-week titration pack
pregabalin (Lyrica) ⁹⁷	DPN: 150 mg/day in three divided doses PHN: 150 mg/day in two to three divided doses Fibromyalgia: 150 mg/day in two divided doses Neuropathic pain associated with spinal cord injury: 150 mg/day in two divided doses	DPN: 300 mg/day PHN: 300 - 600 mg/day Fibromyalgia: 300 - 450 mg/day Neuropathic Pain associated with spinal cord injury: 300 – 600 mg/day	25, 50, 75, 100, 150, 200, 225, 300 mg capsules 20 mg/mL solution
tapentadol ER (Nucynta ER) ⁹⁸	initially 50 mg twice daily (approximately every 12 hours); titrate to response and tolerance within therapeutic range of 100—250 mg twice daily.	500 mg/day	50, 100, 150, 200, 250 mg tablets

CLINICAL TRIALS

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Due to paucity of data, placebo-controlled trials have been included for some categories. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

No studies have been published regarding lidocaine 4%/allantoin 2%/petrolatum 30% (Vexa) topical patch.

Post-Herpetic Neuralgia (PHN)

capsaicin

A large, double-blind, vehicle-controlled study of 143 patients with chronic PHN was performed to evaluate the efficacy of capsaicin 0.075% cream.⁹⁹ Patients with PHN of six months' duration or longer were enrolled. All efficacy variables, including the physician's global evaluation of reduction in PHN pain, changes in pain severity on the categorical scale, visual analogue scale (VAS) for pain severity, visual analogue scale for pain relief, and functional capacity scale, showed significant improvement at nearly all time points throughout the study for capsaicin patients. In contrast, the group receiving vehicle cream remained essentially unchanged. There were no serious adverse effects observed or reported throughout the trial.

To establish the effects of capsaicin on daily activities in patients with painful diabetic neuropathy, 277 men and women with painful peripheral polyneuropathy and/or radiculopathy were enrolled in an eight-week, double-blind, vehicle-controlled study with parallel randomized treatment assignments.¹⁰⁰ Participants were unresponsive or intolerant to conventional therapy and were experiencing pain that interfered with functional activities and/or sleep. Either capsaicin 0.075% cream or vehicle cream was applied to the painful areas four times daily. A visual analogue scale of pain intensity and baseline measurements of the pain's interference with the ability to walk, work, participate in recreational activities, use shoes and socks, sleep, and eat were recorded at onset and at two-week intervals. Statistically significant differences were seen in the percentage of patients with improvement in pain (69.5 percent capsaicin versus 53.4 percent vehicle patients; $p=0.012$), improvement in walking (26.1 versus 14.6 percent, respectively; $p=0.029$), improvement in working (18.3 versus 9.2 percent, respectively; $p=0.019$), improvement in sleeping (29.5 versus 20.3 percent, respectively; $p=0.036$), and

improvement in participating in recreational activities (22.8 versus 12.1 percent, respectively; $p=0.037$).

A multicenter study established the efficacy of capsaicin 0.075% cream in relieving the pain associated with diabetic neuropathy.¹⁰¹ Capsaicin or vehicle cream was applied to painful areas four times daily for eight weeks in 252 patients randomly assigned to one of two groups. Pain intensity and relief were recorded at two-week intervals using physician's global evaluation and visual analog scales. Analysis at the final visit showed statistical significance favoring capsaicin for the following: pain improvement by the physician's global evaluation scale (69.5 versus 53.4 percent, respectively), decrease in pain intensity (38.1 versus 27.4 percent, respectively), and improvement in pain relief (58.4 versus 45.3 percent, respectively). With the exception of transient burning, sneezing, and coughing, capsaicin was well tolerated.

lidocaine 5% patch (Lidoderm)

In a double-blind, crossover trial with 35 patients with post-herpetic neuralgia, lidocaine 5% patch was compared to no treatment for a single dose.¹⁰² Lidocaine performed statistically better than vehicle patch in terms of pain intensity from four to 12 hours. A two-week trial of lidocaine patch versus vehicle patch was performed in a double-blind manner in 32 patients with constant pain who had been considered responders in an open-label lead-in. Lidocaine patch was statistically significantly better than vehicle in terms of time to exit from trial, daily average pain relief, and patient's preference of treatment. Half of the patients also took oral medication commonly used in the treatment of post-herpetic neuralgia, but use was similar between groups.

gabapentin enacarbil (Horizant) and placebo

A double-blind, randomized study was conducted where 115 patients with PHN completed a seven-day baseline period and 11-day gabapentin run-in period.¹⁰³ Eligible patients ($n=101$) were randomized and received a total of 1,200 mg gabapentin enacarbil ($n=47$) or placebo ($n=54$) administered twice daily for 14 days. The remaining patients discontinued from the study before randomization for the following reasons: adverse events, not eligible, not adhering to the protocol, and patient request. Improvement in mean weekly pain scores from baseline to the end of treatment (primary endpoint) was significantly greater for gabapentin enacarbil (-2.1) versus placebo (-1.2), $p=0.0321$. Significant improvements from gabapentin enacarbil versus placebo were also seen in sleep, mood, and patient global assessment ($p<0.05$). Lastly, gabapentin enacarbil provided a significant increase in average steady state gabapentin concentrations versus gabapentin capsules in the same patients ($n=42$; $p=0.005$).

Diabetic Peripheral Neuropathic Pain (DPNP) and Neuropathic Pain (NP)

capsaicin and amitriptyline

An eight-week double-blind, multicenter, parallel study compared the safety and efficacy of capsaicin cream and oral amitriptyline in 235 patients with painful diabetic neuropathy involving the feet.¹⁰⁴ Two hundred thirty-five patients were randomized to treatment. A visual analogue scale of pain intensity and measurements of interference by pain with functional activities were recorded at onset and at two-week intervals. Capsaicin and amitriptyline produced equal and statistically significant improvements in pain over the course of the study. By the end of week eight, 76 percent of patients in each group experienced less pain, with a mean reduction in intensity of more than 40 percent. By the

end of the study, the interference with daily activities by pain had diminished significantly ($p=0.001$) in both groups. No systemic side effects were observed in patients treated with capsaicin. Most patients receiving amitriptyline experienced at least one systemic side effect, ranging from somnolence to neuromuscular and cardiovascular adverse effects.

duloxetine (Cymbalta) and placebo

In a 12-week, multicenter, double-blind study, 457 patients experiencing pain due to diabetic polyneuropathy were randomly assigned to treatment with duloxetine 20 mg once daily, 60 mg once daily, 60 mg twice daily, or placebo.¹⁰⁵ The two higher doses of duloxetine demonstrated statistically significant greater improvement than placebo in the 24-hour mean VAS for pain, the primary efficacy measure, beginning one week after randomization and continuing throughout the 12-week trial. Significantly more patients in all three active-treatment groups achieved a 50 percent reduction in the 24-hour mean VAS for pain compared with placebo. Duloxetine treatment was considered to be safe and well tolerated with less than 20 percent discontinuation due to adverse events. The FDA-approved dosage of duloxetine for DPNP is 60 mg/day.

In a similar study, patients with diabetic peripheral neuropathic pain (DPNP) were randomized to treatment with duloxetine 60 mg once or twice daily or placebo for 12 weeks.¹⁰⁶ Both doses of duloxetine were superior to placebo in reducing the 24-hour average pain severity score. Treatment with duloxetine also resulted in greater improvement in the secondary endpoints of Clinical Global Impression of Severity (CGI-S) and Patient's Global Impression of Improvement (PGI-I). The study was performed by the manufacturer of duloxetine. The FDA-approved dosage of duloxetine for DPNP is 60 mg/day.

tapentadol ER (Nucynta ER) and placebo

A Phase III, randomized-withdrawal, placebo-controlled trial evaluated the safety and efficacy of tapentadol ER versus placebo.¹⁰⁷ The primary outcome was the change in pain intensity from randomization measured by an 11-point numerical rating scale (NRS) taken twice daily. DPN patients ($n=588$) who were dissatisfied with their opioid and/or non-opioid analgesic treatment and scored at least 5 on the NRS (0=no pain, 10=pain as bad as you can imagine) were titrated to an optimal dose of tapentadol ER (100-250 mg twice daily) during a three-week open-label phase. Those patients ($n=395$) who sustained a one-point reduction in their NRS score were randomized to receive placebo or tapentadol ER for a 12-week double-blind phase.

The least-squares mean difference between groups in the change in average pain intensity from the start of double-blind treatment to week 12 was -1.3 (95% CI, -1.7 to -0.92; $p<0.001$, tapentadol ER versus placebo). A total of 60.5 percent of patients reported at least a 30 percent improvement in pain intensity from the start to the end of the open-label titration phase; of the patients who were randomized to tapentadol ER, 53.6 percent reported at least a 30 percent improvement from pre-titration to week 12 of the double-blind phase. The most common treatment-emergent adverse events that occurred during double-blind treatment with tapentadol ER included nausea, anxiety, diarrhea, and dizziness. Potential limitations of this study are related to the enriched enrollment randomized-withdrawal trial design, which may result in a more homogeneous patient population during double-blind treatment and may present a risk of unblinding because of changes in side effects from the open-label to the double-blind phase. Compared with placebo, tapentadol ER 100-250 mg twice daily

provided a statistically significant difference in pain and was well-tolerated by patients with painful DPN.

Fibromyalgia

duloxetine (Cymbalta) and placebo

A 12-week, randomized, double-blind, placebo-controlled trial assessed the efficacy and safety of duloxetine in 354 female patients with fibromyalgia, with or without current major depressive disorder.¹⁰⁸ Patients received duloxetine 60 mg once daily or twice daily or placebo. The primary outcome was the Brief Pain Inventory (BPI) average pain severity score (defined as ≥ 30 percent reduction in this score). Compared with placebo, both duloxetine groups improved significantly more ($p < 0.001$) on the BPI average pain severity score (60 mg daily [55 percent; $p < 0.001$]; 60 mg twice daily [54 percent; $p = 0.002$]; placebo [33 percent]). The treatment effect of duloxetine on pain reduction was independent of the effect on mood and the presence of major depressive disorder. Patients treated with duloxetine 60 mg once daily or twice daily had significantly greater improvement in remaining BPI pain severity and interference scores, Fibromyalgia Impact Questionnaire, Clinical Global Impression of Severity, Patient Global Impressions of Improvement (PGI-I), and several quality-of-life measures. Both doses of duloxetine were well tolerated. Duloxetine doses over 60 mg daily are not FDA-approved for treatment of fibromyalgia. In a similarly designed trial using only duloxetine 120 mg daily, similar results were found.¹⁰⁹

Efficacy and safety of duloxetine in reducing pain severity in 520 fibromyalgia patients with or without current major depressive disorder were evaluated in a six-month, multicenter, randomized, double-blind, placebo-controlled study.¹¹⁰ Patients were randomly assigned to duloxetine (20, 60, or 120 mg) or placebo, administered once daily. After three months, the duloxetine 20 mg group titrated to 60 mg daily. The co-primary outcome measures were the BPI average pain severity score and PGI-I score. Patients treated with duloxetine 120 mg daily improved significantly more on the co-primary outcome measures at three months (change in BPI score [-2.31 versus -1.39, $p < 0.001$] and PGI-I [2.89 versus 3.39, $p = 0.004$]) and at six months (change in BPI [-2.26 versus -1.43, $p = 0.003$] and PGI-I [2.93 versus 3.37, $p = 0.012$]) compared to placebo. Duloxetine 60 mg per day also significantly improved the co-primary measures at three months, but BPI improvement only at six months. Duloxetine was efficacious in patients both with and without major depressive disorder. There were no clinically significant differences among treatment groups in adverse events. Duloxetine doses over 60 mg daily are not FDA-approved for treatment of fibromyalgia.

milnacipran (Savella) and placebo

A multicenter, double-blind, placebo-controlled trial randomized 1,196 patients with fibromyalgia to receive milnacipran 100 mg daily, 200 mg daily, or placebo for 15 weeks.¹¹¹ The two primary endpoints were rates of fibromyalgia composite responders (based on pain diary scores, PGI-Change [PGI-C], and SF-36) and fibromyalgia pain composite responders (based on pain diary scores and PGI-C). Compared with placebo, significantly greater proportions of milnacipran-treated patients were fibromyalgia composite responders (100 mg: $p = 0.01$; 200 mg: $p = 0.02$) and fibromyalgia pain composite responders (100 mg: $p = 0.03$; 200 mg: $p = 0.004$). Milnacipran was associated with significant improvements in pain after one week of treatment (100 mg: $p = 0.004$; 200 mg: $p = 0.04$), global status (PGI-C: $p < 0.001$ for both doses), physical function (SF-36: 100 mg: $p < 0.001$; 200 mg: $p = 0.02$), and fatigue (Multidimensional

Fatigue Inventory: 100 mg: $p=0.04$). The most common adverse events with milnacipran were nausea, headache, and constipation.

Similarly, a 27-week, randomized, double-blind, multicenter study compared milnacipran 100 and 200 mg daily with placebo in the treatment of 888 patients with fibromyalgia and used the same primary endpoints as the above study.¹¹² After three-months of stable dose treatment, a significantly higher percentage of milnacipran-treated patients met criteria as fibromyalgia responders versus placebo (milnacipran 200 mg, $p=0.017$; milnacipran 100 mg, $p=0.028$). A significantly higher percentage of patients treated with milnacipran 200 mg also met criteria as fibromyalgia pain responders versus placebo ($p=0.032$). Significant pain reductions were observed after week one with both milnacipran doses. At 15 weeks, milnacipran 200 mg led to significant improvements over placebo in pain ($p<0.05$), PGI-C ($p<0.001$), and multiple SF-36 domains. Nausea and headache were the most common adverse events reported by milnacipran users.

A double-blind, placebo-controlled trial was performed to assess 1,025 patients with fibromyalgia who were randomized to receive milnacipran 100 mg daily ($n=516$) or placebo ($n=509$).¹¹³ Patients underwent four to six weeks of flexible dose escalation followed by 12 weeks of stable-dose treatment. Two composite responder definitions were used as primary endpoints: 1) achievement of ≥ 30 percent improvement from baseline in the pain score and a rating of "very much improved" or "much improved" on the Patient's Global Impression of Change scale; 2) these two measurements plus improvement criteria for pain and global status, as well as improvement in physical function on the Short Form 36 (SF-36) physical component summary score. After 12 weeks of stable-dose treatment, a significantly greater proportion of milnacipran-treated patients compared with placebo-treated patients showed clinically meaningful improvements on the two-measure composite responder criteria ($p<0.001$) and three-measure composite responder criteria ($p<0.001$). Milnacipran was well tolerated by most patients, with nausea being the most commonly reported adverse event.

pregabalin (Lyrica) and placebo

A multicenter, double-blind, eight-week, randomized clinical trial compared pregabalin 150, 300, and 450 mg daily with placebo in pain, sleep, fatigue, and health-related quality of life in 529 patients with fibromyalgia.¹¹⁴ The primary outcome was the comparison of endpoint mean pain scores, derived from daily diary ratings of pain intensity. Pregabalin at 450 mg/day significantly reduced the average severity of pain in the primary analysis compared with placebo (-0.93 on a 0-10 scale, $p\leq 0.001$), and significantly more patients in this group had ≥ 50 percent improvement in pain at the endpoint (29 versus 13 percent in the placebo group; $p=0.003$). Dizziness and somnolence were the most frequent adverse events.

The efficacy of pregabalin in patients with chronic lumbosacral radiculopathy was evaluated in a randomized, controlled trial that included a run-in phase to screen out placebo responders, a 28-day, single-blind phase to identify pregabalin responders, a double-blind period to randomize responders to pregabalin or placebo (35 days), and a final medication taper phase of seven days.¹¹⁵ The primary endpoint was time to loss of response during the double-blind phase (one-point increase in pain, discontinuation, or rescue-medication use). In the single-blind phase, 58 percent of patients had at least a 30 percent reduction in pain. In the double-blind phase, pregabalin ($n=110$) and placebo ($n=107$) groups did not differ significantly in time to loss of response. Adverse events caused the discontinuation of 9.9 and 5.6 percent of pregabalin-treated and placebo-treated patients, respectively.

META-ANALYSES

A Cochrane Review was conducted to examine the efficacy and safety of topical lidocaine (Lidoderm) in the treatment of postherpetic neuralgia.¹¹⁶ Three trials involving 182 topical lidocaine-treated participants and 132 control participants were included. Two trials gave data on pain relief, and the remaining study provided data on secondary outcome measures. A meta-analysis combining two of the three studies identified a significant difference between the topical lidocaine and control groups for the primary outcome measure: a mean improvement in pain relief according to a pain relief scale. Topical lidocaine relieved pain better than placebo ($p=0.003$). There were a similar number of adverse skin reactions in both treatment and placebo groups.

The efficacy of antidepressants in the treatment of fibromyalgia was determined by performing a meta-analysis of randomized, placebo-controlled trials with TCAs, SSRIs, SNRIs, and MAOIs.¹¹⁷ Eighteen randomized controlled trials (median duration, eight weeks; range, four to 28 weeks) involving 1,427 patients were included. Overall, there was strong evidence for an association of antidepressants with reduction in pain, fatigue, depressed mood, sleep disturbances, and improved health-related quality of life. Effect sizes for pain reduction were large for TCAs, medium for MAOIs, and small for SSRIs and SNRIs.

SUMMARY

Limited comparative head-to-head data exists on neuropathic pain. Moreover, various professional guidelines suggest different first-line and second-line treatments based on the indication. These include tricyclic antidepressants (TCAs), gabapentin (Gralise, Horizant, Neurontin), pregabalin (Lyrica), opioids, lidocaine 5% transdermal patches (Lidoderm), duloxetine (Cymbalta), and topical capsaicin.

Vexa patch, which contains lidocaine 4%, is indicated for the temporary relief of pain associated with minor cuts, scrapes, and minor skin irritations. It is also approved for scar management and the protection of minor cuts, scrapes, and burns.

Duloxetine (Cymbalta), milnacipran (Savella), and pregabalin (Lyrica) are FDA-approved for the treatment of fibromyalgia. Gabapentin and TCAs have also been shown to be effective.

Duloxetine should be avoided in severe renal impairment whereas gabapentin, milnacipran (Savella), and pregabalin may be options that require dose adjustments. Lidocaine patches (Lidoderm) and the SNRIs, duloxetine and milnacipran, should be avoided in hepatic impairment.

More evaluation is needed in the area of neuropathic pain to determine the most effective treatments. When prescribers choose to try pharmacologic therapy in the treatment of neuropathic pain, there are several options. However, with the lack of comparative data, as well as placebo-controlled trials to judge by, selecting a drug to initiate cannot be done based on clinical effectiveness alone. A prescriber's choice should include other factors such as approved indications, adverse event profiles of the products, ability to treat comorbidities, drug to drug interactions, and contraindications.

Although duloxetine and pregabalin have acquired multiple indications, the potential of other available drugs should not be ruled out. Finally, tapentadol ER (Nucynta ER) should only be initiated for diabetic peripheral neuropathy when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

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